REMARKS

Summary of Invention

The invention features an isolated protein comprising the amino acid sequence of CED-3 (SEQ ID NO:19).

Summary of Office Action

Examination of claim 6 is reported in the present Office Action. Claim 6 was rejected under 35 U.S.C. 112, first paragraph. This rejection is addressed below.

Double Patenting Rejection

Claim 6 was rejected under the judicially created doctrine of non-obviousness-type double patenting as being unpatentable over claim 1 of issued U.S. patent 5,962,301. This rejection will be addressed after allowable subject matter has been indicated, if appropriate.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 6, which is directed to a CED-3 protein, was rejected as lacking enablement. The Examiner asserts that applicants fail to teach how to make and use the claimed protein, basing this rejection on two grounds: (i) that the specification fails to disclose methods of producing a full length CED-3 protein; and (ii) that the specification fails to disclose a use for the CED-3 protein. In support of the enablement rejection, the Examiner cites Xue et al. (Genes and Development 10:1073-2083, 1996, hereafter

"Xue") and Wu et al. (J. Biol. Chem. 272:21449-21454, 1997); references purported to demonstrate that one skilled in the art cannot produce a full-length CED-3 protein in *E. coli*.

Xue

Turning first to Xue, while the Examiner cites Xue in support of the assertion that applicants have failed to enable the production of full length CED-3, the Examiner acknowledges that a full-length CED-3 protein can be produced using a rabbit reticulocyte lysate expression system. With respect to the production of full length CED-3 protein in the reticulocyte lysate system, the Examiner states, "While the *art* taught production of full-length protein by *in vitro* translation in a rabbit reticulocyte lysate, the *specification* does not teach such a method . . . "(emphasis added, Office Action mailed March 14, 2003, page 4, first paragraph).

Contrary to the Examiner's suggestion, applicants' specification is *not* required to teach what is known in the art. This point is made clear in *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with information known in the art* without undue experimentation (emphasis added).

Thus, the teachings present in applicants' specification must *not* be considered in a vacuum; applicants' disclosure must be considered in light of the information known to one skilled in the art at the time of filing. As acknowledged by the Examiner, methods

for the *in vitro* production of polypeptides were known to the skilled artisan at the time of filing. This is further evidenced in Exhibits A (Hunter et al., J. Biol. Chem. 250:409-417, 1975), B (Shapiro et al., J. Biol. Chem. 250: 1759-1764, 1975), and C (Rhoads et al., J. Biol. Chem. 248:2031-2039, 1972), papers that were published nearly twenty years before applicants' earliest priority date, and which describe the use of rabbit reticulocyte lysates for *in vitro* protein production.

For example, Exhibit A states, "All types of double-stranded RNA (dsRNA) tested inhibit *protein synthesis in rabbit reticulocyte lysates* (page 409, left column, first paragraph);" Exhibit B states, "ovalbumin mRNA was purified 90 to 100-fold over oviduct polysomal RNA as judged by both the rate of hybridization to a complementary DNA and by translation in *a rabbit reticulocyte lysate protein-synthesizing system* (page 1759, left column, first paragraph);" and Exhibit C states, "Procedures are described for the quantitative assay of ovalbumin mRNA in a *rabbit reticulocyte lysate protein-synthesizing system* (page 2031, left column, first paragraph). As methods for the *in vitro* synthesis of proteins were clearly known to the skilled artisan at the time applicants' application was filed, it is not necessary for applicants to disclose such methods in their specification. On this point, the M.P.E.P. 2164.01 states, "A patent need not teach, and preferably omits, *what is well known in the art. In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)." (Emphasis added.) Thus, Xue fails to provide support for the enablement rejection.

Wu

Turning next to Wu, the Examiner states:

> Yet another post filing art similarly was not able to express and isolate the full length protein (see Wu et al. J. Biol. Chem. 272:21449-21454, 1997). While the investigators in this art used a mutant to produce a full length Ced-3 protein, the specification does not provide any teaching as to what modification in *ced-3* sequence would have been required to produce the full-length protein (Office Action mailed March 14, 2003, page 4, last paragraph).

Contrary to the Examiner's assertion, Wu does *not* require a mutation to produce a full-length Ced-3 protein, rather Wu intentionally uses a mutant CED-3 to study CED-3's interaction with CED-4, because the wild-type CED-3 protein induces apoptosis in mammalian cells. On this point, Wu states:

> Because CED-3 induces apoptosis in mammalian cells, we used a catalytically *inactive* mutant of CED-3 (CED-3-Flag-G360S) to study the interaction of CED-3, CED-4, and CED-9 (emphasis added, page 21450, right column, first paragraph).

This flag tagged CED-3 mutant is referred to as CED-3 mt-Flag in the labels of Figures 4A and 4B to differentiate it from wild-type CED-3.

Wu expresses the 56 KDa catalytically *active* CED-3 protein to study CED-3 activation by CED-4. Wu states, "293T cells...were transiently transfected with 5μg of plasmids producing *Flag-tagged CED-3*, Myc-tagged CED-4, and HA-tagged CED-9 (Figure 4A's legend, page 21453). With respect to Figure 4A, Wu states:

> As shown in Fig. 4A, expression of CED-3 resulted in partial *processing of the immature 56-kDa CED-3-FLAG protein* as determined by the detection of the mature p13 and p15 products of CED-3.

Thus, Wu *does* express the full-length catalytically active CED-3 protein in mammalian cells. Such methods are taught in applicants' specification, at page 19, lines 20 to 26, where applicants state:

> The activity of the agents can be verified both by *in vivo* bioassays using nematodes which express various forms of *ced-3, ced-4,* or related genes, as described above, and by *in vitro* systems, in which *the genes are expressed in cultured cells*. . . (emphasis added).

In sum, applicants' specification, in view of known art in the field, clearly enables the skilled artisan to produce a CED-3 polypeptide. Accordingly, this basis for the enablement rejection should be withdrawn.

In addition, the Examiner asserts that applicants' specification fails to teach how to use a CED-3 protein. On this point, the Examiner states:

> While the specification has disclosed vaguely about using the protein, for example, on page 3, lines 13-18, the specification states "This invention further relates to methods for altering....the activity of the cell death genes or their encoded products in cells..." or on page 7, in the section on detailed description of the invention, the specification states "The activity of a cell death gene is intended to include the activity of the gene itself and of the encoded products of the genes. Thus, agents...include those which affects the expression as well as the function of the encoded RNA and protein..." or on page 19, in the section on testing of agents, the specification states "The activity of the agent can be verified both by in vivo bioassays...and by in vitro systems, in which the genes are expressed in the cultured cells or in which the isolated or synthetic gene products are tested directly in biochemical experiments", the specification does not provide any specific teaching as to how to use the protein (Office Action mailed March 14, 2003, page 5, first paragraph).

Applicants disagree. In addition to the uses cited by the Examiner, at page 3, lines 1 and 2, applicants teach that the protein encoded by the *ced-3* gene may be used to generate antibodies. Methods of producing recombinant proteins and antibodies directed

against CED-3 proteins are provided in applicants' specification as originally filed, for example, at page 29, lines 15-33.

Applicants further disclose that the CED-3 polypeptide can be used in drug screening, to identify agents that increase or decrease the activity of CED-3. At page 2, line 32, to page 3, line 18, applicants teach

> This invention further relates to methods for altering (increasing or decreasing) the activity of the cell death genes or their encoded products in cells and, thus, for altering the proliferative capacity or longevity of a cell population or organism.

Methods of drug screening are provided at pages 17-20, where applicants describe nematode bioassays that can be used to identify CED-3 agonists and antagonists. Applicants further disclose, page 20, lines 26-33,

> Such agents are useful for treating (i.e., for both preventive and therapeutic purposes) disorders and conditions characterized by cell deaths, including neural and muscular degenerative diseases, stroke, traumatic brain injury, myocardial infarction, viral (e.g., HIV) and other types of pathogenic infections, as well as cell death associated with normal aging and hair loss.

Moreover, while applicants disagree with the Examiner's characterization of the uses of the polypeptide cited by the Examiner as "vague," applicants note that the M.P.E.P. states:

> As long as the specification discloses *at least one method for making and using* the claimed invention of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (emphasis added). M.P.E.P. 2164.01(b)

Moreover, if a statement of utility in the specification contains within it *even a connotation of how to use the claimed invention* then the enablement requirement of 35 U.S.C. 112 is satisfied (2164.01(c) M.P.E.P) (emphasis added). Applicants' specification

as originally filed plainly teaches at least one use of the claimed CED-3 polypeptide. Thus, this basis for the enablement rejection may be withdrawn.

In sum, the skilled artisan provided with applicants' specification and using no more than routine methods could plainly make and use the claimed invention. Thus, the enablement rejection may be withdrawn.

CONCLUSION

Applicants submit that this case is in condition for allowance, and such action is respectfully requested. If the Office does not concur, a telephonic interview with the undersigned is hereby requested.

Enclosed is a petition to extend the period for replying for three months, to and including September 15, 2003, since September 14, falls on a Sunday.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 9/15/03

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